BIODEFENSE RESEARCH SUPPORTING THE DoD: A NEW STRATEGIC VISION

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FOREWORD

The general public often assumes that medical products will be available to members of the U.S. armed forces in harm's way. Availability of safe and effective drugs and vaccines, however, is never an accident; such products are the fruition of focused and methodical research, testing and evaluation over many years. Medical research is inherently a high risk endeavor, and even the most efficient programs can span almost 15 years and cost over $1 billion from product discovery to Food and Drug Administration licensure.

In this monograph, Colonel Coleen Martinez examines the productivity of the Department of Defense's biodefense research program over the course of more than 35 years, coupled with changes in the global research environment since the events of September 11, 2001. Few will argue the need for a national investment in biodefense. Where the deployment of a biologic agent of mass destruction is largely an unpredictable risk, the outcome certainly could be catastrophic for an unprotected population. An urgent moral imperative is cast upon the federal government, then, to objectively assess the application and management of its biodefense research resources.

The purpose of this monograph is not to provide a single solution, but rather to stimulate senior leader critical analysis, dialogue and action to improve program efficiency and productivity for the benefit of both the warfighter and the nation. The Strategic Studies Institute is pleased to publish it as a contribution to the debate on this important subject.

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SUMMARY

The Department of Defense (DoD) has had a unique mission in biological defense research over the past 4 decades. Throughout this history, the military biological disease threats were relatively straightforward, there was little urgency linked to successful product fielding, there was no mechanism by which to gain Food and Drug Administration (FDA) product licensure, and there was little competition for mission or funds. In the post-September 11, 2001 (9/11) environment, however, the scope of potential threats has increased immeasurably, relative funding for the DoD has decreased, urgency to field solutions has skyrocketed, the FDA has provided a way forward to product licensure, and active non-DoD players in this arena have grown exponentially, aligning with newly designated, congressionally mandated funding sources. The old paradigms that governed the DoD research program structure and mission are no longer viable in this changing environment. This monograph examines the current organization of the DoD biodefense research program in light of the changing national biodefense landscape and industry best practices, and argues that all aspects of the DoD biodefense program should be consolidated with all other federal biodefense resources, including those within the National Institutes of Health, to create a single, focused, and productive program. This new agency, subordinate to the Department of Health and Human Services, will be positioned and equipped to provide medical solutions to the warfighter on the battlefield, as well as to U.S. citizens.

BIODEFENSE RESEARCH SUPPORTING THE DoD: A NEW STRATEGIC VISION

INTRODUCTION

> He who every morning plans the transaction of the day and follows out that plan, carries a thread that will guide him through the maze of the most busy life. But where no plan is laid, where the disposal of time is surrendered merely to the chance of incidence, chaos will soon reign.
>
> Victor Hugo
> French dramatist, novelist, and poet (1802-85)

Since President Richard M. Nixon declared the end of the U.S. offensive biological research program in 1969,[1] the U.S. Department of Defense (DoD) has pursued a research program strictly for defensive purposes, with the primary objective being development of products to protect the warfighter on the battlefield. DoD, after almost 4 decades of investment in a biological defense program, has contributed significantly to the scientific knowledge base and has produced more than two dozen candidate pharmaceutical products. Three of these candidates are currently in advanced development within the DoD, some have been assumed by the National Institute of Allergy and Infectious Disease (NIAID) for further development, several are no longer being developed and are available for use only as Investigational New Drugs (INDs, also referred to as "investigational"), several have been dropped completely from development, and several still languish in the technical scientific base awaiting a DoD decision on further investment.[2]

Gaining Food and Drug Administration (FDA) licensure of products is a difficult task, requiring demonstration of the product's safety and effectiveness for the stated indication of use. Before 2002, licensing biodefense pharmaceutical products was an impossible task because, for obvious reasons, it was unethical or impracticable to conduct human clinical trials for efficacy. Such testing required challenging a person who had received the developmental medical product with a biological threat agent to demonstrate that the product actually prevented or treated the disease. Recognizing this barrier to licensure, and coincident with a heightened need for biodefense preventive and therapeutic countermeasures, the FDA approved the "animal rule" in 2002.[3] The animal rule allows for licensure in the absence of human efficacy testing, if at least one (more likely two) surrogate animal models faithfully representing human infection and disease caused by the authentic biological agent are available and provide sufficient data to suggest that the product will act similarly in humans.

Approval of the animal rule by the FDA was critical to DoD, since only 4 years earlier, in the midst of Gulf War Syndrome concerns, DoD had been cited in a Government Accounting Office report with numerous deficiencies in its ability to administer investigational products (products approved only for testing in humans and not yet licensed by the FDA for general use) in an operational environment.[4] Subsequently, in response to both safety and public perception concerns regarding DoD's use of investigational products in service members, the Deputy Secretary of Defense directed DoD to use licensed products preferentially over investigational products, and ruled that a presidential waiver was required in the event that an

investigational product was to be used in the absence of an obtained informed consent.[5] Aligning with these events, the medical biodefense mission appeared to be clear: develop FDA-licensed medical countermeasures to protect the warfighter from biological warfare threats.

The faltering productivity of the DoD biodefense program, despite its world-class infrastructure, talented workforce, and well-defined acquisition framework, appears to be directly related to its convoluted, unnecessarily complex, and circuitous chains of authority with regard to pharmaceutical development coupled with insufficient management, oversight, and accountability. Similarly, U.S. fiscal resources increasingly are poured into non-DoD medical biodefense research without any overarching plans to orchestrate these investments into licensed products. The nation requires a clean excision of all medical biodefense resources from within the federal government and consolidation under a new agency birthed specifically to support efficient product development.

CHALLENGES OF PHARMACEUTICAL DEVELOPMENT

The Industry Model.

Development of pharmaceutical products is a long, complex process. Industry, including small biotechnology companies, out of necessity, has been most efficient at defining and negotiating the pathway of medical product discovery, development, and acquisition. Even using best business practices, however, the average timeline from discovery to FDA licensure currently is 14 years[6] and requires an

investment between $800 million (M) and $1.6 billion (B) per product.[7] One of the most significant total-cost drivers for development is the high number of candidate failures for each successfully developed and marketed product, reflecting the technical risk inherent in pharmaceutical product research.

The major elements of product development are candidate discovery; preclinical studies (laboratory and animal); clinical trials (human safety and human or animal efficacy); product manufacturing, characterization, and release; and FDA IND and licensure submissions. One estimate describes a pathway beginning with 10,000 candidates, of which 250 succeed in entering preclinical studies, of which only five make it to late-stage clinical trials, after which one passes the stringent licensing requirements.[8] The most effective way to reduce both the timeline and cost associated with finding the winning product is to manage the development closely and to identify the failures and discontinue those efforts as early in the process as possible, so that resources can be refocused on the remaining contenders.[9]

Industry Management.

The issue of identifying and abandoning losing candidate products early is extremely important, but not simple. There is a fine balance between killing a promising candidate too early, when perhaps some retooling could have transformed it into a success, versus the temptation to continue to pour resources into a candidate that is failing in the hope that it can be revived. These difficult management decisions require program leaders who are qualified and experienced not only in the science to understand the technical data and appropriately interpret the risks, but also in

pharmaceutical and business acquisition requirements, to corporately assess the approach from a programmatic perspective.

Industry best practice places "a single empowered and accountable individual (project manager) in charge of the program" and ensures "focused [not diffuse] cross-functional management . . ."[10] The corporate executives empower interdisciplinary management teams who are charged to meet prospective and well-defined milestones, and who are given the flexibility to manage their resources (e.g., personnel and budget) to attain their goals. To earn this flexibility, the teams are held accountable to meeting their milestones and are rewarded for success. In the technology base, higher-level management reviews typically occur on a quarterly basis.[11] The straightforward management chain and minimal layers from the highest position down to the lowest echelon of operations are apparent in Figure 1.

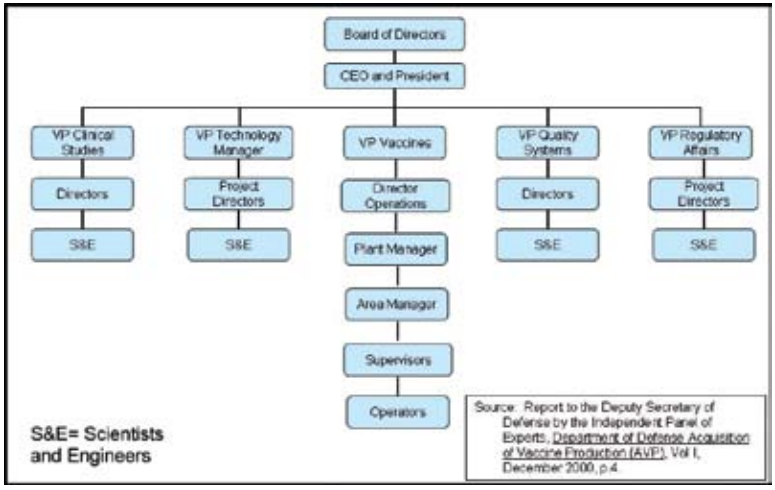


Figure 1. Simplified Organizational Chart Depicting a Generic Industry Model for a Pharmaceutical Company Dedicated to Vaccine Development.

CHALLENGES OF THE DoD BIODEFENSE ACQUISITION SYSTEM

Leadership.

Congress, over the last decade, has questioned the management and productivity of the DoD's biodefense medical product-development program. Congressional concerns have led to a number of commissioned studies by panels of national pharmaceutical experts to analyze the DoD system and proffer recommendations for decreasing development risk and improving efficiencies and success rates.[12] It is puzzling that despite the repeated emergence of common themes in the study outcomes such as recognition of "disjointed and ineffective management"[13] and an organizational structure that is unnecessarily complex and counterproductive[14] and quite explicit recommendations with regard to the same, the DoD has not improved the research and development program substantially in accordance with any of these recommendations. Such Department nonresponsiveness in the face of clear congressional intent to address risk reduction in an extremely high-priority program area leads the author to believe the only explanation is that the recommended solutions are "too hard to do." The DoD is like the giant sloth, too large, heavy, and slow to be able to transform its structure and processes. The sloth "moves very slowly and only if necessary";[15] similarly, there has been no compelling reason for the DoD to choose to move to improve its biodefense medical product development program substantially, because, despite its lack of response, its programs continue to receive funding. One significant obstacle is that many key DoD leadership positions lack individuals knowledgeable

in, and appreciative of, the complexities of medical product development. Although many recent strategic documents stress the critical importance and high priority of the biodefense program,[16] there appears to be a tacit acceptance that once the leaders validate the program's criticality, then "a miracle will occur" and licensed products will begin to appear. Without an appreciation of the structure and management changes necessary to improve efficiency and effectiveness in this complicated and lengthy endeavor, there is no impetus for the wholesale transformation, which the experts deem as indispensable to an effective program. The "high priority" assigned to the DoD's biodefense research program wanes when the leaders are faced with difficult decisions with regard to organization and resourcing.

Management.

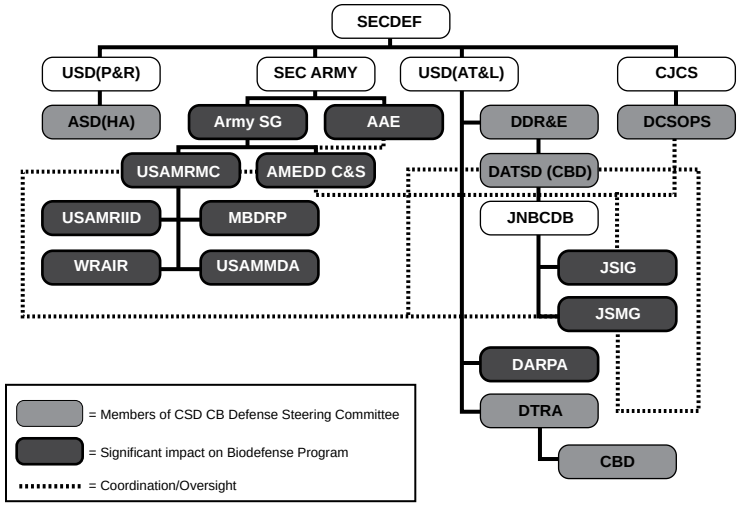
As referenced above, a repeated criticism of the DoD biodefense program is its fragmented organizational structure. In contrast to the streamlined industry model previously illustrated in Figure 1, the DoD's research and development structure is complex and diffuse, with many stakeholders. Before 2004, the Army as executive agent bore primary responsibility for managing and executing the DoD's biodefense program. The Army Medical Department Center and School had responsibility for requirements, the Joint Services Management Group had oversight of products, and the Joint Program Executive Officer for the newly-formed Joint Program Executive Office for Chemical and Biological Defense (reporting through the Army Acquisition Executive to the Defense Acquisition Executive) managed the chemical and biological material acquisition process.

The Defense Advanced Research Projects Agency (DARPA) additionally devoted significant funding to medical biodefense discovery efforts (ranging from over $60M in Fiscal Year (FY)01 to $45M in FY04[17]), but there was no mandate to coordinate these projects with, or to feed their outcomes into, the Army's biodefense program. There was a limited DARPA program from FY01-05 in which approximately $40M of funds was available to support transition of candidate products into more mature development efforts.[18] These "transition" funds were awarded competitively by the DoD to extramural research contracts, however, with none designated for intramural use to seed initiation of potential new programs borne of successful DARPA projects. The net result of this 5-year investment has been no integration of any promising DARPA efforts into the DoD's medical acquisition system.[19]

Nonpharmaceutical biodefense research efforts, such as those developing personal protective equipment and sensors, fell directly under the Under Secretary of Defense for Acquisition, Technology, and Logistics, and were managed by the Defense Threat Reduction Agency. Fueled by concerns that programs were not coordinated and integrated sufficiently, the Under Secretary of Defense for Acquisition, Technology, and Logistics directed the Assistant to the Secretary of Defense (Nuclear and Chemical and Biological Defense Programs) to "assign responsibility for management and integration of all CB Science and Technology efforts . . . to the Defense Threat Reduction Agency" in 2002.[20] Despite good intentions, this solution exacerbated the fragmentation of the program management by reinforcing a chasm between the DoD's technology base and advanced development stages of the program. This management change also opened the technology base beyond the DoD's laboratories

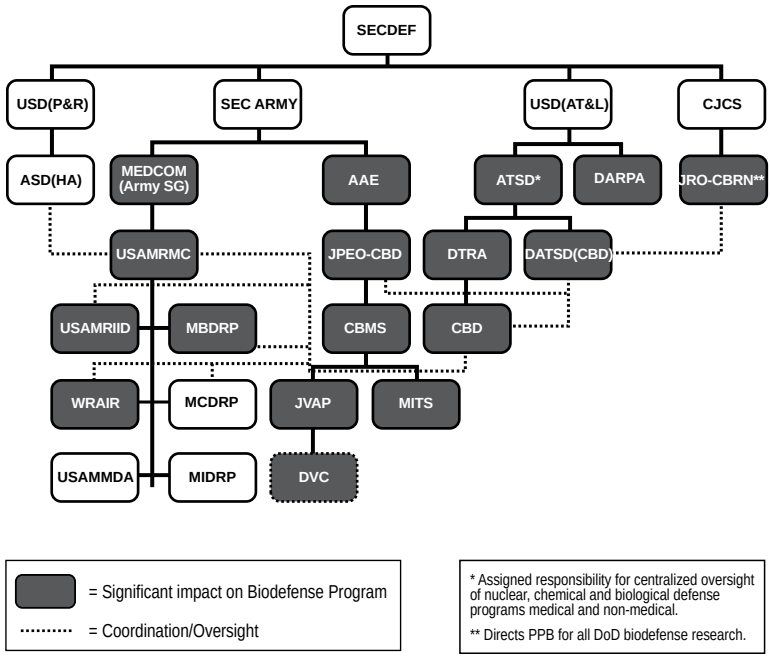
to allow any organization performing biodefense research to compete for funding and eventual entry of its candidate product into the DoD acquisition system. Effectiveness of implementing this potentially positive change, however, was tempered by the lack of any overarching development plans. The net impact, therefore, was dilution of program fiscal resources across a larger candidate base, still without a plan to focus and follow-through on specific candidates (DoD or non-DoD).

The issue of fragmented organizational program structure was cited as a significant obstacle to program success in program evaluations such as the Report of a Panel of Experts in 2000[21] and the Institute of Medicine Report on DoD Vaccine Acquisition in 2002.[22] Based on an unwieldy program structure (Figure 2),[23] the Institute of Medicine study panel recommended consolidating all DoD elements conducting medical biodefense research. The DoD indeed did respond to the recommendations, as subsequently mandated by Congress, by extracting all elements of the program previously managed by the Army as lead agent for this effort and relocating them under the DoD offices for program management and direction (Figure 3).[24] The congressional intent spanned beyond the medical biodefense program and was an attempt to consolidate all medical and nonmedical aspects of the program, bringing them under common oversight. The congressional mandate did, in fact, bring aspects of biodefense medical and non-medical programs under DoD oversight, but in so doing had the untoward secondary effect of creating an even more diffuse and convoluted management system for pharmaceutical development. Instead of streamlining the structure, this reorganization only served to move drug and vaccine development further away from the industry best practices model.



AAE, Army Acquisition Executive;
AMEDD C&S, Army Medical Department Center and School;
Army SG, Army Surgeon General;
ASD(HA), Assistant Secretary of Defense for Health Affairs;
CBD, Director Chemical Biological Directorate;
CJCS, Chairman, Joint Chiefs of Staff;
DARPA, Defense Advanced Research Projects Agency;
DATSD(CBD), Deputy Assistant Secretary of Defense, Chemical and Biological Defense Programs;
DCSOPS, Deputy Chief of Staff for Operations;
DDR&E, Director of Defense Research and Engineering;
DTRA, Defense Threat Reduction Agency;
JSIG, Joint Service Integration Group;
JSMG, Joint Service Materiel Group;
MBDRP, Medical Biological Defense Research Program;
SEC ARMY, Secretary of the Army;
SECDEF, Secretary of Defense;
USAMMDA, U.S. Army Medical Materiel Development Activity;
USAMRIID, U.S. Army Medical Research Institute of Infectious Diseases;
USAMRMC, U.S. Army Medical Research and Materiel Command;
USD(AT&L), Under Secretary of Defense for Acquisition, Technology and Logistics;
USD (P&R), Under Secretary of Defense for Personnel and Readiness;
WRAIR, Walter Reed Army Institute of Infectious Diseases.

Figure 2. Simplified Organizational Chart Depicting DoD Biodefense, Pre-2004.



AAE, Army Acquisition Executive;
AMEDD C&S, Army Medical Department Center and School;
Army SG, Army Surgeon General;
ASD(HA), Assistant Secretary of Defense for Health Affairs;
ATSD, Assistant to the Secretary of Defense;
CBD, Director Chemical Biological Directorate;
CBMS, Chemical Biological Medical Systems;
CJCS, Chairman, Joint Chiefs of Staff;
DARPA, Defense Advanced Research Projects Agency;
DATSD(CBD), Deputy Assistant Secretary of Defense, Chemical and Biological Defense Programs;
DCSOPS, Deputy Chief of Staff for Operations;
DDR&E, Director of Defense Research and Engineering;
DTRA, Defense Threat Reduction Agency;
DVC, Dynport Vaccine Company (DoD prime systems contractor);
JRO-CBRN, Joint Requirements Office for Chemical, Biological, Radiological and Nuclear Defense;
JVAP, Joint Vaccine Acquisition Program;
MBDRP, Medical Biological Defense Research Program;
MCDRP, Medical Chemical Defense Research Program;

Figure 3. Simplified Organizational Chart Depicting DoD Biodefense, Post-2004 (continued).

MEDCOM, U.S. Army Medical Command;
MIDRP, Military Infectious Diseases Research Program;
MITS, Medical Identification and Treatment Systems;
SEC ARMY, Secretary of the Army;
SECDEF, Secretary of Defense;
USAMMDA, U.S. Army Medical Materiel Development Activity;
USAMRIID, U.S. Army Medical Research Institute of Infectious Diseases;
USAMRMC, U.S. Army Medical Research and Materiel Command;
USD(AT&L), Under Secretary of Defense for Acquisition, Technology and Logistics;
USD (P&R), Under Secretary of Defense for Personnel and Readiness;
WRAIR, Walter Reed Army Institute of Infectious Diseases

Figure 3. Simplified Organizational Chart Depicting DoD Biodefense, Post-2004 (concluded).

As a result of the 2004 reorganization, management of the DoD medical biodefense program became split among four primary organizations. The Army laboratories (primarily the U.S. Army Medical Research Institute of Infectious Diseases for biodefense products) were still the primary executors of the program, but were divested of any programmatic decision authority. The management of the technical base and advanced development research was now divided between the Defense Threat Reduction Agency (subordinate to the Under Secretary of Defense for Acquisition, Technology, and Logistics) and the Joint Program Office (subordinate to the Army Acquisition Executive). The Joint Requirements Office (under the Chairman, Joint Chiefs of Staff, Force Structure, Resources, and Assessment Directorate) was now responsible for program requirements and planning, programming, budget, and execution (PPBE) activities. Coordination of product development across the divide between these organizations does not appear to exist in any

measurable degree, and there is little to no corporate agreement on product planning, or even product requirements (to be addressed in more detail under the Requirements section). The Joint Requirements Office, Defense Threat Reduction Agency, and Joint Program Office representatives initiated triad meetings with an objective of attempting to coordinate the program. However, at least from the perspective of the executing laboratories, there has been little to no improvement and no tangible and clear guidance birthed from these periodic meetings. The result of this leadership and management void is inefficient use of the DoD's biodefense resources, including infrastructure and personnel. In the absence of a coordinated effort directed from a corporate level (which appeared to be the intent of the reorganization), the laboratory researchers are most apt to follow their own interests, and an extremely competitive, rather than cooperative, research environment divides rather than unites the efforts.

Furthermore, the current structure and absence of any coherent and coordinated corporate development plan creates an environment that allows, or even encourages, political influence and decisions based on issues other than customer requirements, science, program plans, and risk analysis. Individuals without requisite knowledge or experience in pharmaceutical product development are placed in high-level, decisionmaking positions. When approached to consider special funding set-asides, such individuals' inability to review critically and discuss the scientific data, coupled with a lack of a prospectively-defined decisionmaking process, leaves them vulnerable to being influenced by whoever can tell them a convincing story. By occupying high level positions, they gain

the authority to unilaterally decide to direct millions of dollars to fund specific efforts. The programmatic impact of such political influence is to dilute program resources of funding and personnel that could or should be devoted to higher priority efforts and also to set the conditions for unnecessary duplication of approaches and poorly coordinated efforts. Even if a new project has the potential to be a valuable addition to the overall program, the effort should not be considered in a vacuum, but rather be integrated fully into an overarching plan and assigned to the most qualified (rather than the most politically connected) individual(s).

Finally, a noteworthy problem with the current the DoD biodefense program management, and in stark contrast to the industry model, is that there is no "bottom line" about which one needs to worry. There is no necessity to define or meet any developmental milestones. Program funding continues year after year, regardless of program productivity in fielding useable countermeasures for the warfighter. Although the 2004 DoD biodefense reorganization was intended to improve coordination and oversight, the lack of qualifications and experience at the reviewer level allowed programs that should have been terminated to persist instead, based simply on promises of future performance, rather than scientific data and risk analysis. In spite of all of the DoD-mandated program reviews and oversight, there is a dearth of those participating in the reviews who have the experience and knowledge to critically assess the presentation, data, conclusions, or recommendations. There is, therefore, a façade of accountability, but in fact there is no accountability required, unlike industry with the need to justify expenditures and investments with the shareholders.

The diffuse program structure, lack of coherent and focused plans, and absence of qualified program managers described above caused a lack of urgency in tracking programs through to fruition, that is, availability of licensed products. This inevitably left the DoD unprepared when faced with crises of heightened biological warfare or terrorist threats, such as may be present in military conflict and/or war. Historically, such times of national crisis stimulate sudden interest in pushing all available technologies out to the deployed soldier, and there is a predictable call to assess all medical products still in the developmental pathway, to determine if any exist that might be able to undergo rapid fielding. While this approach is effective with regard to weapons systems, vehicles, and body armor, for example,[25] it is not a preferred solution for medical products. Attempting to field unlicensed medical products for the purpose of force protection has been fraught with difficulty and controversy.[26] Although the actual safety risk to service members receiving such an unlicensed product would likely be low (because such products generally would have an established safety profile, with only unproven efficacy), there is a more significant risk that recipients of such products would falsely perceive that they have protection that may not exist. The greatest risk, however, is the DoD's credibility and reputation with the FDA and the public. It is demonstrated repeatedly that when the DoD attempts to administer unlicensed products in a deployed environment, it is unable to meet the stringent recordkeeping and protocol requirements of the FDA. Protocol violations then become the subject of Government Accounting Office investigations, negative publicity, and public suspicion, all of which unnecessarily blemish a well-intended program.

Rather than exerting pressure to get new medical solutions in the field at the time of national crisis, the DoD program leaders would be better off to demand, from their research laboratories, a persistent urgency to field products and a focused management of the research effort to meet this end. Considering the long timelines associated with product development and licensure, even in the best and most efficient programs, biodefense research cannot afford the luxury of months, years, or decades of unfocused and poorly managed programs.

Impact of the Organizational Structure.

Issues spanning the entire biodefense product development pathway reflect shortcomings of the fragmented program structure described above and depicted in Figure 3. The U.S. Army Medical Research Institute of Infectious Diseases is the DoD's primary biodefense research laboratory, employing over 800 staff, with access to 40,500 net square feet of biosafety level (BSL)-3 and 6,700 net square feet of BSL-4 biocontainment laboratory space, necessary for research on the world's most dangerous pathogens. The U.S. Army Medical Research Institute of Infectious Diseases' scientists, many of whom are leaders in their fields, have significantly contributed to biodefense. With regard to product successes, however, developmental timelines far exceed industry standards, and the ability of the DoD to see product development through to product completion is diminished by opportunities for efforts to become derailed primarily due to ineffective coordination among offices, disagreement on requirements and priorities, lack of prospectively defined developmental milestones and decision points, or funding instability (Figure 4).[27]

Product	Development Timeline	Status	Current Program Manager	Comments	Success
Vaccine 1	Tech base: 9 years (1996-2004) MSA: 2004 MSB: 2005	In advanced development: One of two competing products (the other being a non-DoD candidate) for upcoming downselect decision (2006)	JVAP	Lab was slow to assume vaccine mission; lost 2 years; now in jeopardy of lagging behind competitor	Unknown at this time
Vaccine 2	Tech base: 8 years (1993-2000) MSA: 2000	In advanced development: licensure planned for 2012	JVAP	Could have been ready for transition sooner but lab continued basic research in lieu of vaccine focus	Future DoD?
Vaccine 3	Tech base: 8 years (1993-2000) MSA: None; JVAP did not have funding	Product stalled. No development plan	None; JVAP plan for sequential development had timeline out to ~2018.	NIAID funded continued research on one serotype, but unknown if this will continue	None
Vaccine 4	Tech base: 4 years (~1993-1997) MSA: 1998	No POM funding recommended (FY 2008-2013).	JVAP (but will change to "none" if POM recommendation is approved.)	In June 2006 the JRO unexpectedly removed future funding from this product (FY 2008-2013 POM submission) and terminated a successful advanced development program.	None
Vaccine 5	Tech base: 18+ years (1989-today) MSA: None; JVAP does not have funding	No POM funding recommended (FY 2008-2013). Ready to transition in 2006, now a 2008 UFR	JSTO	Tech base timeline lengthened by failure to kill 1st and 2nd generation products early. USAMRIID now working on 3rd generation vaccine effort.	None
Vaccine 6	Tech base: ~6 years (1990-1996) MSA: None	Dropped by the DoD (PI deceased)	DHHS (CDC)	JVAP assumed when stood up office (1996) but later transferred to NIAID	NIAID has funded to small degree in the past, but no active program.
Vaccine 7	Tech base: 16+ years (1991-today) MSA: 1996, product disapproved	Inactive. Not funded by JSTO. No POM funding for CMBS. MRMC legal trying to license to non-DoD pharmaceutical company; CBMS/JSTO now unsure if they want to retain it instead?	None	1996: CBMS MDA concerned re: incapacitation versus lethality protection	None (possible future technology transfer?)

Figure 4. Product Outcomes from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), DoD's Biodefense Lead Laboratory (continued).

Vaccine 8	Tech base: ~15 years (1960's-70's) MSA: None	This vaccine may be difficult to license; product characterization barriers. Product available only under IND.	None for current (1st generation) IND vaccine	NIAID has funded GMP manufacture and phase I clinical trial when picked up product from JVAP. Clinical trial data not complete yet. But NIAID unlikely to continue development past Phase 1 even if this is a good product. There is no requirement for Vaccine 8 in the national stockpile, so there would be no Bioshield dollars available for further development and procurement. NIAID has begun funding of 2nd generation vaccine effort (still in discovery phase).	Limited (IND product)
Vaccine 9	Tech base: 14+ years (1986-1996; then 1998-2002) MSA: None	MRMC licensed to Company A; NIAID now funding	NIAID (through initial phase II trials), then DHHS (ORDC) for procurement	Army directed to cease program in 1996 (1st generation vaccine available); resurrected in 1998 (1st generation vaccine adverse events); licensed to Company B in 2002	Technology transfer from the DoD to NIAID (NIAID also has 2nd candidate, non-DoD origin)
Vaccine 10	Tech base: ~10 years (1970's) MSA: None	Made in 1970s and 1980s at Company C; never made again in future	None	SIP use	Limited (IND product)
Vaccine 11	Tech base: ~10 years (1970's) MSA: None	Made in 1970s and 1980s at Company C; never made again in future	None	SIP use	Limited (IND product)
Therapeutic Drug 1	Tech base: 9+ years (~1998-today) MSA: None	Studies ongoing; CBMS has been planning on transition . . . Drug is already licensed for another indication; seeking new label indication.	JSTO	Requirement not clear; slow lab progress; uncontrolled/ unmanaged program; PI disagreement on experimental design conditions	None

CBMS, Chemical Biological Medical Systems;
CDC, Centers for Disease Control and Prevention;
GMP, Good Manufacturing Practices;
IND, Investigational New Drug;
JSTO, Joint Science and Technology Office for Chemical and Biological Defense;
JVAP, Joint Vaccine Acquisition Program;
MDA, Milestone Decision Authority;
MSA, milestone A (decision point to continue acquisition program into the Technology Development phase);
MSB, milestone B (decision point to continue acquisition program into the system development and deployment phase);
NIAID, National Institute of Allergy and Infectious Disease;
ORDC, Department of Health and Human Services Office of Research and Development Coordination;
PI, principal investigator;
POM, Program Objective Memorandum;
SIP, Special Immunizations Program;
UFR, unfunded requirement.

Figure 4. Product Outcomes from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), DoD's Biodefense Lead Laboratory (concluded).

One such example is the current fate of a vaccine against Threat Agent 5 (Figure 4, row 5). The U.S. Army Medical Research Institute of Infectious Diseases has received funding to research Threat Agent 5 in the technology base for over 18 years. This research culminated in FY06 in candidate Vaccine 5 with demonstrated efficacy in a nonhuman primate model; a candidate that appears to be sufficiently mature for a transition to advanced development (Chemical Biological Medical Systems Joint Project Management Office). The Chemical Biological Medical Systems Joint Project Management Office has been unsuccessful in securing a funding wedge for this vaccine candidate in the Program Objective Memorandum (POM) beginning in FY06. POM preparation is the responsibility of the Joint Requirements Office, an office which is completely dissociated from the product developmental efforts. The Defense Threat Reduction Agency, now viewing this vaccine as a mature candidate, appears to be unlikely to continue to fund the effort beginning in FY07.[28] Candidate Vaccine 5, therefore, despite the millions of dollars and years of manpower devoted to bringing it to the cusp of success, is perched precariously on the edge of transition from the Defense Threat Reduction Agency to Chemical Biological Medical Systems Joint Project Management Office and is in serious danger of dropping into the abyss between these organizations. The scientific base is left without important initial testing in humans, a vital step in the developmental pathway necessary to validate the medical approach and all of the preclinical research invested in the product up to that point. Most importantly, the warfighter is left without the chance of having a licensed product to protect against this threat.

The development of a vaccine to protect against Threat Agent 7 provides a second example (Figure

4, row 7). The U.S. Army Medical Research Institute of Infectious Diseases received funding to conduct technology base research on protection against this threat for over 16 years. In 1996, the U.S. Army Medical Research Institute of Infectious Diseases presented its candidate Vaccine 7 to the advanced developer for a milestone A transition decision (decision point to continue an acquisition program into the Technology Development, or "advanced development" phase). The Milestone Decision Authority at that time disapproved the transition, because of concerns about the requirements for this product. There is no record, however, of concern over requirements from the office responsible for requirements generation, at that time, the Army Medical Department Center and School (see Figure 2).

Vaccine 4 provides yet a third recent example. Until June 2006, this candidate's developmental pathway showcased how the medical acquisition system *should* work. After a mere 4 years of technology base research (1993-97), candidate Vaccine 4 smoothly transitioned to the advanced developer (Chemical Biological Medical Systems Joint Project Management Office) as a result of a favorable milestone A acquisition decision. Although its continued development was somewhat resource-constrained, projected funding was sufficient to fulfill a plan for obtaining product licensure in 2014. A completely unanticipated turn in the program occurred in June 2006, however, when the Joint Requirements Office recommended removing all Vaccine 4 funding from its FY 2008-13 POM submission. Although the FY 2008-13 POM recommendations are not yet finalized, at this late stage in the process the prediction is that the Joint Requirements Office's decision will stand. Without warning, the DoD's Vaccine 4 development

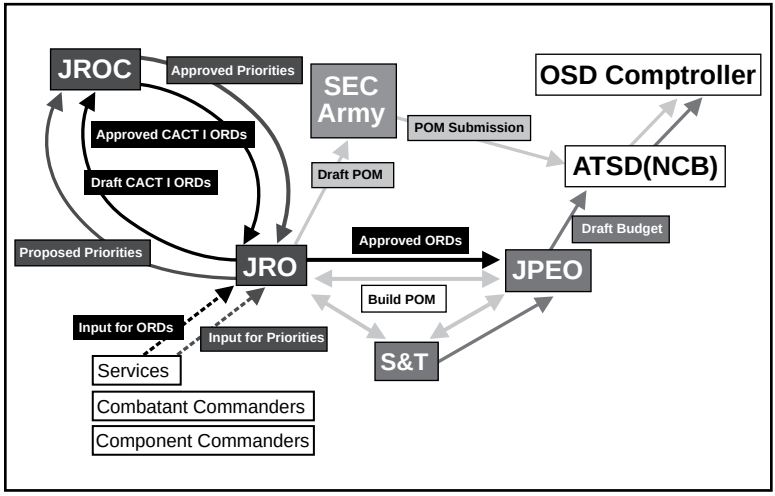
program was thereby effectively terminated, based on unknown criteria of which a scientific review of the product does not appear to have been a part.

The consistent themes that resonate throughout the product failures such as these are poor requirements documentation, a lack of an overarching plan, and ineffective coordination between organizations. These weaknesses often result in potential products getting delayed or dropped mid-development and in managers who are unable to negotiate the transitions, or product hand-offs.

Requirements.

Another challenge of the DoD pharmaceutical acquisition system is a clear articulation of requirements. The Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear Defense has the responsibility of identifying gaps and proposing solutions that it defines as requirements (or required capabilities) in one of four Joint Capabilities Integration and Development System documents. The document that guides research in the technology base (pre-Milestone A) is the broadly written Initial Capabilities Document, which should propose "a prioritized list of non-materiel and materiel approaches to provide the desired joint warfighting capability."[29] In fact, a Joint Requirements Office information brief illustrates the approval process for program priorities (Figure 5),[30] but interestingly, this process appears to involve only the combatant commanders, Joint Requirements Office, and Joint Requirements Oversight Council; there is no indication of prioritization subsequently being passed down to the Joint Program Office and Science and Technology program offices that should be managing the research

programs. One could presume that these priorities would be delineated in the Joint Requirements Office's requirements documents, but unfortunately, the Initial Capabilities Documents applicable to biodefense pharmaceutical research, defining warfighter needs for prophylaxes[31] and therapeutics,[32] to prevent and treat disease, respectively, neither specify nor prioritize disease-causing agents of interest.



ACAT, Acquisition Category;
ATSD(NCB), Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs;
JPEO, Joint Program Executive Office;
JRO, Joint Requirements Office;
JROC, Joint Requirements Oversight Council;
ORD, Operational Requirements Document (now replaced by Capability Development Documents, CDDs);
OSD, Office of the Secretary Defense;
POM, Program Objective Memorandum;
S&T, Science and Technology.

Figure 5. JROC-Approved JRO-CBRN Defense Process.

In the transition from a biodefense research program based on a prioritized, validated threat list, to capabilities-based requirements,[33] the program gained flexibility but lost focus. Specification of priorities is vital to making wise programming and budgeting decisions. The current void of research priorities results in funds being spread broadly across a large number of research areas, rather than being centered on a few areas ranked as most important. Lack of focus equates to slow progress, even, at times approximating Brownian motion.

THE CHANGING NATIONAL LANDSCAPE FOR BIODEFENSE

Funding.

Before 2001, there was not a large federal investment in biological defense research and development and the funds that were devoted to that mission primarily resided within the DoD. This reflected the Cold War-era perception that the only significant risk of biological attack was to deployed warfighters and not to the U.S. civilian population. The DoD was the lead agency in biological defense, and the U.S. Army Medical Research Institute of Infectious Diseases was its primary executing laboratory. The annual DoD budget for biological defense research averaged approximately $60M from FY99 to FY01.[34]

After the events of 9/11 and the post-9/11 anthrax letters, the U.S. populace recognized its vulnerability to biological terrorism, and the governmental response was to direct a significantly increased investment toward protection against purported biological threats.[35] Those within the DoD's biological defense

research and development circle predicted that the Army would be designated as recipient and manager of these funds. Shockwaves echoed through the DoD's biodefense community when it found instead that the National Institutes of Health (NIH) under the Department of Health and Human Services (DHHS) would be the recipient of the majority of this budget increase and assume the role as the lead federal agency for developing biodefense countermeasures.[36]

This was indeed an interesting twist of fate. Before 2001, in spite of the criticism of the effectiveness of the DoD's medical biodefense management, the DoD was still the only federal department with measurable experience or success in medical product development. Development of products was a completely new mission for the NIH, whose laurels rested on its ability to conduct basic research and contribute immensely to the academic body of literature and general knowledge base. One could speculate on the basis for this decision and whether or not the DoD's inability to reform its structure and management of the program as repeatedly recommended by expert panels and the Government Accounting Office[37] perhaps tainted confidence in the DoD to manage an even larger program. Another possibility reflects the perception that there is a major difference in the countermeasures needed for the military's protection versus that of the civilian population. Because the NIH mission centers on public health, the funds provided for research to develop countermeasures to protect U.S. citizens logically could be seen as falling within the NIH domain, rather than that of the DoD.

As illustrated in Figure 6,[38] where the DoD assumed a modest post-9/11 increase in annual biodefense funding of approximately $30M, the DHHS annual

budget increased over $1500M. The DoD was suddenly neither the sole player nor even the major player in this research domain. The NIH responded to its new mission quickly, producing the NIAID Strategic Plan for Biodefense Research in February 2002.[39]

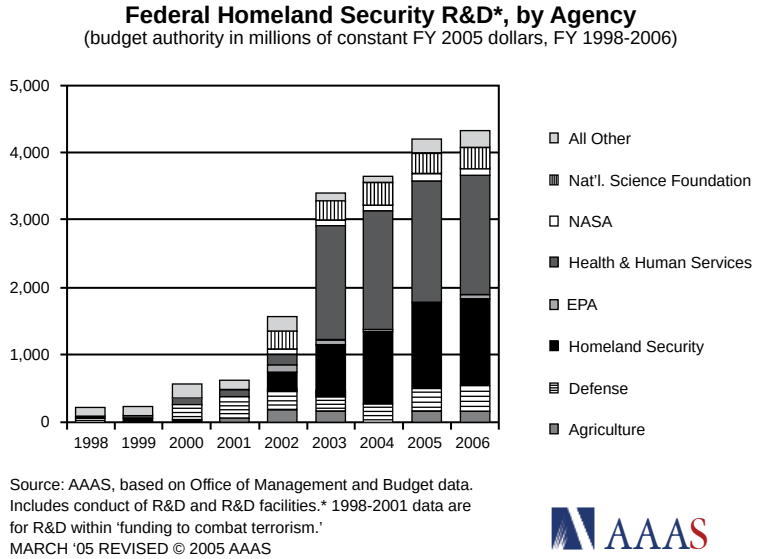


Figure 6. Federal Homeland Security Research and Development Funding, by Agency (in $M).

Various offices and individuals within the DoD biodefense research program acted quickly to position themselves to be able to leverage DoD knowledge and research and development resources to compete for NIAID funding. Any coordination that did take place however, was generally at an individual level. There was no overarching plan to integrate DoD and NIAID biodefense efforts. To the contrary, NIH grants policies actually presented obstacles to DoD scientists. The NIH policy prohibits federal institutions from receiving

grant funds for Facilities and Administrative expenses and salaries for permanent federal employees.[40] It is therefore impossible for a DoD scientist to conduct research using the NIH grant mechanism unless that individual is able to justify that same research need to a second, discrete customer who is willing to cost share and provide the salary and laboratory overhead funds to support that work.

The DoD, primarily at the U.S. Army Medical Research Institute of Infectious Diseases, has unique and critical infrastructure, biocontainment capabilities, and intellectual capacity in biowarfare and bioterrorist threat agents at a concentration unequalled anywhere else in the world. The DoD does not, however, receive a budget equivalent to the scope of its mission and does not have the structure and processes in place to manage its limited funds efficiently.

Biodefense Participants.

The infusion of over $1.5B per year into medical biodefense countermeasure research has resulted in an exponential increase in the scientific investigators and institutions interested in taking on a biodefense mission. "Fund it, and they will come." In the pre-9/11 era, the DoD had a corner on this market, but since 2002 the NIH has been able to stimulate tremendous national interest in biodefense research both within academia, through competitive grant awards for basic (early) research, and also in industry, through contract awards, generally for advanced research on more mature candidate products. Yet another new funding mechanism, Project Bioshield (with an available $5.6B over 10 years for procurement of biodefense countermeasures for the national stockpile[41]), has drawn

limited interest of some additional pharmaceutical industry players.

Certain aspects of biodefense research require specialized biocontainment laboratories, especially for studies of disease pathogenesis and countermeasure effectiveness. The highest level of laboratory biocontainment security is BSL-4, followed by BSL-3. Recognizing the national infrastructure shortfall of BSL-3 and -4 space needed for this expanded biodefense mission, a portion of the NIH funds is designated for the development of Regional Centers of Excellence (BSL-3), Regional Biocontainment Laboratories (BSL-3), and National Biocontainment Laboratories (BSL-4) over the next 5 years. A total of 10 Regional Centers of Excellence, 13 Regional Biocontainment Laboratories, and two National Biocontainment Laboratories currently are planned by the NIAID, to be located strategically across the country as foci of biodefense expertise. Before this expansion of infrastructure, only the U.S. Army Medical Research Institute of Infectious Diseases and the Centers for Disease Control and Prevention (hereafter referred to as the Centers for Disease Control) in Atlanta, Georgia, had BSL-4 laboratory space in the United States, and only the U.S. Army Medical Research Institute of Infectious Diseases was devoted to biodefense product development. When all of these new facilities are completed, they collectively will contain approximately the total containment space available at the U.S. Army Medical Research Institute of Infectious Diseases. This doubling of capability still means, however, that the U.S. Army Medical Research Institute of Infectious Diseases will no longer hold a unique niche.

With the development of increased competition in the field of biodefense research over the near term, the DoD's programs, without substantial reform, are in

danger of losing prominence and the ability to make substantial contributions.

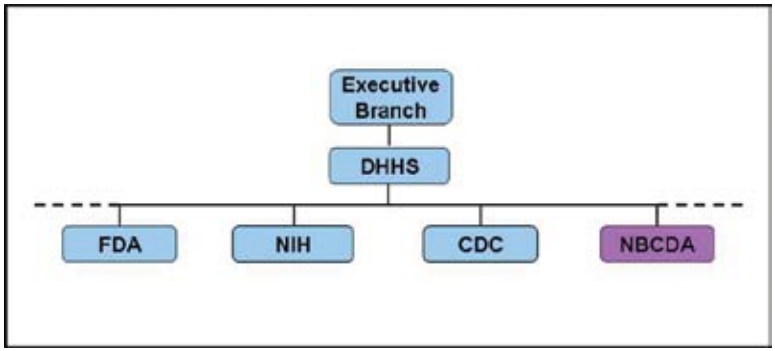
RECOMMENDATIONS

Recommended Action.

The U.S. military and the nation require medical countermeasures to prevent and treat disease that would result from the intentional use of biological agents. Pharmaceutical development, even in the best and most efficient circumstances, is a long and complex process. The DoD, despite its unique infrastructure, intellectual firepower, and decades of experience, has many obstacles blocking its road to success, such as a diffuse organizational structure, lack of a single program leader, managers without the necessary qualifications and experience, and the absence of any overarching plans. Despite numerous program reviews and specific recommendations for program improvement, the DoD has been either unwilling or unable to improve the program structure to position it for success.

The NIAID, under the NIH, recently has received a large budgetary increase to support a new public health biodefense mission. There are more similarities than differences between the NIH and the DoD missions, and there is no clear justification as to why these programs must remain distinct. The NIAID has a distinguished history in funding basic research, but has no history or experience in product development. Even within the NIAID, although the biodefense strategic plan calls for development and licensure of products, it has neither prioritized this mission nor modified its organization sufficiently to reflect the best [industry] business practices required to achieve this goal.

It is in the best interest of both warfighter protection and homeland defense to consolidate all national biodefense research and development resources under a single organization. This organization would be of sufficient size, complexity, and mission priority that it should be granted agency status under DHHS[42] as the National Biological Countermeasure Development Agency (NBCDA) (see Figure 7). All biodefense resources of both the DoD (e.g., Defense Threat Reduction Agency and DARPA chemical and biological defense research programs involving pharmaceutical development; the Chemical Biological Medical Systems Joint Project Management Office; the U.S. Army Medical Research and Materiel Command's Medical Research Institute for Infectious Disease, and resources of its Walter Reed Army Institute of Research involving chemical and biological defense pharmaceutical development; see Figure 3) and relevant offices and branches of DHHS (e.g., the NIH, DHHS, and its Office of Research and Development Coordination, and Centers for Disease Control), including budgets, personnel, and infrastructure should be assigned to the NBCDA. In so doing, the reassigned individuals and facilities must lose their previous organizations' identities and become completely unified (not simply co-located) and focused, from the agency's inception, on a singular mission.



Organizational structure depicting placement of the proposed NBCDA.

CDC, Centers for Disease Control and Prevention;
DHHS, Department of Health and Human Services;
FDA, Food and Drug Administration;
NBCDA, [proposed new] National Biological Countermeasure Development Agency;
NIH, National Institutes of Health.

Figure 7. Proposed New Agency for National Biological Countermeasure Development.

In establishing this new agency, it is essential to recognize the lessons learned from the DoD, NIH, and the pharmaceutical industry. The new agency must adopt a structure and management that will be streamlined, flexible, and efficient, with delineation of management and resources devoted to discovery work (best patterned after the NIH model) and product development (best patterned after the industry model).

Risks and Risk Mitigation.

Reorganization that does not reflect an improvement in the ability to accomplish the mission is detrimental

to programs. If the NBCDA is not created with prospective thought and planning, the end result could be even further degradation of productivity.

The NBCDA must have a clear mission statement articulated even before the first individual is assigned. The mission of this organization is to develop biological countermeasures. Ultimate success is measured only through fielding of these products. With all assigned personnel understanding the vision and mission up front, their energies can better be immediately devoted toward teaming cooperatively to discover solutions.

The NBCDA must be created with a clear organizational structure, containing minimal layers in its hierarchy, with a single responsible individual at the top who is accountable for the entire program.

It is vital that key positions be filled with individuals fully qualified and experienced in both the science and business of pharmaceutical product development. That individuals who are either politically, rather than scientifically, qualified, or merely available, could be placed in leadership and management positions is a high risk.

A risk-mitigation strategy to ensure clarity of vision, organizational structure, and the hiring of sufficiently qualified staff would be for the government to constitute and seek the advice of an external review committee, comprised of experts in pharmaceutical product research and development, drawn from both industry and academia,[43] during the development of the NBCDA. Guidance provided by this body would be invaluable both during the formative stages of the agency and throughout its future operation.

A risk related to hiring the most qualified individuals is the inability of the federal government to offer salaries, benefits, and incentives that are competitive

with industry. At this time, the relative inflexibility of hiring options within this system makes this risk one that the government cannot easily mitigate and would have to accept.

Another potential risk of transferring all biological defense research and development out of the DoD is that the mission of the NBCDA might not cover all aspects of the current DoD program adequately, nor specifically address military requirements. In the past, there was a significant difference in the military approach to biowarfare protection and the civilian approach to protection against bioterrorism. The military favored development of vaccines to limit morbidity on the battlefield and maintain a functional warfighting force. Vaccines were seen as a solution which could be applied to the entire military population, being a relatively small force. Recent experience with anthrax and smallpox vaccines and fallout related to Gulf War illnesses, however, demonstrate that the vaccine policy regarding the total military force is difficult to apply. The civilian approach favors therapeutics, administered on a limited basis only to those known to be exposed to an agent. As the military has begun to recognize the impracticality of mass vaccinations and limitations regarding specificity of vaccines to a single agent versus potentially broader activity of therapeutics, the military is shifting away from vaccines and embracing therapeutics. Therefore this past divergence of missions already is narrowing. Currently, the DoD requirements[44] appear to be almost identical to those delineated in the NIAID Strategic Plan.[45]

Two other areas in which the DoD biodefense program contributes, are providing biodefense training and conducting disease outbreak investigations.

Both training and global outbreak response clearly fall within the Centers for Disease Control mission,[46] however, so the military's involvement in these domains might be viewed as duplicative. As long as the biodefense elements of the Centers for Disease Control are subsumed into the NBCDA, these missions would continue without need for dedicated DoD involvement.

It is important to ensure availability of assignments within the NBCDA for both military biomedical scientists and clinicians, so the military would not lose its expertise, which is necessary to maintain to support military deployments. Interagency agreement between the DoD and NBCDA should permit cross-assignment of personnel to maintain military skills and benefit from continued DoD contributions to the national medical biodefense effort.

CONCLUSION

The DoD has tremendous and unique resources and skills that could contribute immensely toward developing critically needed countermeasures against biological weapons. Poor DoD program organization and management, however, have resulted in a dysfunctional program with little success in measurable outcome. While DHHS has a significantly increased budget for a biodefense mission closely duplicative to that of the DoD and, while the NIH (within DHHS) has a stellar reputation with regard to basic academic research, DHHS is inexperienced and unproven in its ability to develop products. Pharmaceutical product development is a long, complex process and requires special organizational structure, highly qualified leadership and management, and long-term and

stable resourcing, including funding. The United States would benefit greatly by the consolidation of all federal biodefense resources into a new agency under the DHHS, specifically designed to meet the stringent demands of product development.

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